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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MIKKEL THANING and RENE IN'T ZANDT[1]

Appeal 2016-004796
Application 11/572,679
Technology Center 1600

Before MELANIE L. McCOLLUM, JEFFREY N. FREDMAN, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods for discriminating between health and tumor tissue, which have been rejected as being directed to non-statutory subject matter and as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] Appellants' identify the Real Party in Interest as GE Healthcare AS. Appeal Br. 2.

STATEMENT OF THE CASE

> Magnetic resonance (MR) imaging (MRI) is a imaging technique that has become particularly attractive to physicians as it allows for obtaining images of a patients [sic] body or parts thereof in a non-invasive way and without exposing the patient and the medical personnel to potentially harmful radiation such as X-ray.

Spec. 1, ll. 9–12. MRI is particularly useful for imaging soft tissue and organs. *Id.* at 1, ll. 13–14,

MRI tumor imaging may be carried out using contrast agents which enables smaller tumors to be detected. *Id.* at 1, ll. 17–22. The present Specification describes a method using hyperpolarized ^{13}C-pyruvate to improve tumor imaging. *Id.* at 1, ll. 5–7.

Claims 1–6 and 9–19 are on appeal. Claim 1 is representative of the rejected claims and reads as follows:

> 1. A method for the discrimination between healthy and tumour tissue, said method comprising:
>
> (a) acquiring ^{13}C-MR images of ^{13}C-pyruvate and its ^{13}C-containing metabolite alanine and its ^{13}C-containing metabolite lactate from a subject pre-administered with a composition comprising hyperpolarised ^{13}C-pyruvate,
>
> (b) correcting the lactate image for the amount of pyruvate and/or alanine by multiplying the lactate image by the inverted pyruvate and/or alanine image, a high image signal within said corrected lactate image(s) being indicative of tumour tissue.

The claims have been rejected as follows:

Claims 1–6 and 9–19 have been rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter.

Claims 1, 2, 4–6, 10, and 11 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Hara[2] in view of Ardenkjaer-Larson[3], Poptani[4] and Busch.[5]

Claim 3 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Hara in view of Ardenkjaer-Larson, Poptani and Busch in further view of Gibson.[6]

Claims 9–19 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Hara in view of Ardenkjaer-Larson, Poptani, Busch, and Gibson in further view of King.[7]

Claims 1, 2, 6, 9–13, and 17–19 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ke[8] in view of Minko[9] and Ardenkjaer-Larson.

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[2] Hara and Yokoi, *Difference of ^{14}C turnovers in brain and in transplanted glioma after intravenous injection of ^{14}C-1-pyruvate into rats*, 12 EUR. J. NUCL. MED. 249–51 (1986) ("Hara").
[3] Ardenkjaer-Larson et al., US 6,278,893 B1, issued Aug. 21, 2001 (Ardenkjaer-Larson").
[4] Poptani et al., *Cystic Intercranial Mass Lesions: Possible Role of In Vivo MR Spectroscopy in its Differential Diagnosis*, 13:7 MAG. RES. IMAG. 1019–29 (1995) ("Poptani").
[5] Busch, *Studies on the Metabolism of Pyruvate-2-C^{14} in Tumor-bearing Rats*, 15 CANCER RES. 365–74 (1955) ("Busch").
[6] PHARMACEUTICAL PREFORMULATION AND FORMULATION, A PRACTICAL GUIDE FROM CANDIDATE DRUG SELECTION TO COMMERCIAL DOSAGE FORM 333 (Mark Gibson ed., Interpharm/CRC) (2001) ("Gibson").
[7] King, US 2002/0167316 A1, published Nov. 14, 2002 ("King").
[8] Ke et al., US 6,617,169 B2, issued Sept. 9, 2003 ("Ke").
[9] Minko et al., *Efficacy of the Chemotherapeutic Action of HPMA Copolymer-Bound Doxorubicin in a Solid Tumor Model of Ovarian Carcinoma*, 86 INT. J. CANCER 108–17 (2000) ("Minko").

Claims 5 and 16 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ke in view of Minko and Ardenkjaer-Larson in further view of Hara.

Claims 4 and 13 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ke in view of Minko, Ardenkjaer-Larson and Hara in further view of Poptani.

Claims 3 and 14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ke in view of Minho, Ardenkjaer-Larson, Hara, and Poptani in further view of Gibson.

NON-STATUTORY SUBJECT MATTER

Issue

The issue is whether a preponderance of evidence supports the Examiner's finding that claims 1–6 and 9–19 are directed to non-statutory subject matter.

The Examiner finds the present claims are directed to a natural principle in that they are based on a naturally occurring correlation between the levels of a metabolite and the presence of a condition such as cancer. Final Act.[10] 18. The Examiner finds that the "further steps are merely conventional methods of diagnosis used in the field." Final Act. 21

Appellants contend that the use of a labeled pyruvate as well as detecting the labeled metabolites cannot be considered a natural principle. Appeal Br. 15. Appellants also contend that the application of the correction

[10] Final Office Action mailed April 2, 2015 ("Final Act."); Non-Final Office Action mailed Sept. 4, 2014 ("Non-Final Act.").

factor in not merely an application of a natural principle. *Id.* Appellants contend that the application of the correction factor is something significantly more than application of a natural principle. Reply Br. 7. Appellants argue that the Examiner has failed to put forth any evidence to support the conclusion that the steps recited in the claims are routine in the field. Appeal Br. 16.

Analysis

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

35 U.S.C. § 101 states that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

The Supreme Court has "long held that this provision contains an important implicit exception: Laws of nature, natural phenomena, and abstract ideas are not patentable." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014).

Our reviewing court has summarized the Supreme Court's two-part test for distinguishing between claims to patent-ineligible exceptions, and claims to patent-eligible applications of those exceptions, as follows:

> Step one asks whether the claim is "directed to one of [the] patent-ineligible concepts." [*Alice*, 134 S. Ct. at 2354]. If the answer is no, the inquiry is over: the claim falls within the

> ambit of § 101. If the answer is yes, the inquiry moves to step two, which asks whether, considered both individually and as an ordered combination, "the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo* [*Collaborative Services v. Prometheus Labs, Inc.*, 132 S. Ct. 1289, 1297 (2012)]).
>
> Step two is described "as a search for an 'inventive concept.'" *Id.* (quoting *Mayo*, 132 S. Ct. at 1294). At step two, more is required than "well-understood, routine, conventional activity already engaged in by the scientific community," which fails to transform the claim into "significantly more than a patent upon the" ineligible concept itself. *Mayo*, 132 S. Ct. at 1298, 1294.

Rapid Litigation Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1047 (Fed. Cir. 2016) (paragraphing added).

In the present case, claim 1 recites the steps of "acquiring ^{13}C-MR images of ^{13}C-pyruvate and its ^{13}C-containing metabolite alanine and its ^{13}C-containing metabolite lactate from a subject" followed by "correcting the lactate image for the amount of pyruvate and/or alanine by multiplying the lactate image by the inverted pyruvate and/or alanine image." Appeal Br. 22 (Claims App'x). We agree with Appellants that the claims present something significantly more than a natural phenomenon. In particular, we agree with Appellants that the correction of the lactate image using the inverse of the pyruvate and/or alanine image presents something more than an application of a natural principle. Appeal Br. 15.

We analogize the step of "correcting the lactate image" to the rubber curing process in *Diamond v. Diehr*, 450 U.S. 175 (1981). Just as in *Diehr*, "the respondents [did] not seek to patent a mathematical formula. Instead, they [sought] patent protection for a process of curing synthetic rubber." *See id.* at 187. Here, the Appellants seek protection for a specific process of

tumor identification whose ordered combination adds an analysis step that is not routine and conventional. .

Comparing claim 1 to the claim at issue in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 US 66, 7475 (2012), step (a) in claim 1 is similar to the administering step (a) in *Mayo*, where a compound known to exist is administered to a subject of interest. *Id.* at 74. The final clause of step (b) of claim 1 in which a "high image signal within said corrected lactate image(s) being indicative of tumour tissue" is similar to step (b) in *Mayo* correlating the drug level to administration amounts. *Id.* at 75.

However, the first clause of step (b) of claim 1, "correcting the lactate image for the amount of pyruvate and/or alanine by multiplying the lactate image by the inverted pyruvate and/or alanine image", is something more than an instruction to administer ^{13}C-pyruvate and does not preempt all administrations of ^{13}C-pyruvate, all tumor identification methods, or all image correction processes, but rather is a patent-eligible combination of these technologies. As evidenced by our obviousness analysis below, we do not believe that a technology must be unobvious to be patent eligible.

In sum, for the reasons discussed, Appellants persuade us that a preponderance of the evidence fails to support the Examiner's conclusion that Appellants' claim 1 is patent-ineligible under § 101. Accordingly, we reverse the Examiner's rejection under 35 U.S.C. § 101.

OBVIOUSNESS

Hara combined with Ardenkjaer-Larson, Poptani and Busch

Issue

The issue with respect to this rejection is whether a preponderance of the evidence supports the Examiner's conclusion that claims 1, 2, 4–6, 10, and 11 would have been obvious over Hara combined with Ardenkjaer-Larson, Poptani, and Busch under 35 U.S.C. § 103(a).

The Examiner finds that "Hara discloses a method for detecting tumors in vivo by administering ^{14}C or ^{11}C pyruvate into rats and watching the turnover of pyruvate to lactate, alanine, and bicarbonate." Non-Final Act. 4. The Examiner also finds that Hara teaches that a buildup of lactate is indicative of tumor cells. *Id.* The Examiner finds that Hara teaches "collecting images of the lactate and pyruvate with the highest lactate signal indicating the presence of a tumor." *Id.*

The Examiner finds that Ardenkjaer-Larson teaches the use of hyperpolarized agents to improve MRI signals and that the agent can be ^{13}C labeled pyruvic acid. Non-Final Act. 5. The Examiner finds that Poptani teaches the acquisition of images for metabolites such as pyruvate and lactate and the use of metabolite ratios to grade tumors. *Id.* at 6. The Examiner finds that Busch teaches using labeled pyruvate to detect tumors and that the ratio of lactate to pyruvate in tumors is 20:1 compared to 1:1 in normal tissues. Non-Final Act. 7. The Examiner concludes that:

> It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use a known ratio for identifying tumors, the lactate/pyruvate ratio taught by Busch in a method for identifying tumors by using the metabolism of pyruvate as taught by Hara, Ardenkjaer-Lars[o]n, and Poptani. This is merely the combination of a known technique for

> identifying tumors with a method for identifying tumor tissues. The skilled artisan would [have] predicted that this combination would function effectively as . . . all the methods are directed at imaging tissues, particularly tumor tissues, and the measurement [of] individual metabolites and ratios of metabolites was already known to be useful in grading and identifying tumors.

Id. at 7.

Appellants contend the references, either alone or in combination, do not teach or suggest the use of the claimed image correction. Appeal Br. 7–9. Appellants also contend that there is no motivation to combine the references. *Id.* at 10–11.

Analysis

We adopt the Examiner's findings of fact, reasoning on scope and content of the prior art, and conclusions set out in the Final Action and Answer regarding this rejection. We find the Examiner has established that claim 1 would have been obvious over Hara combined with Ardenkjaer, Poptani, and Busch. Appellants have not produced evidence showing, or persuasively argued, that the Examiner's determinations on obviousness are incorrect. Only those arguments made by Appellants in the Briefs have been considered in this Decision. Arguments not presented in the Briefs are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015). We address Appellants' arguments below.

Appellants contend that the references do not teach or suggest the image correction recited in the present claims. Appeal Br. 9–10. We are unpersuaded. As the Examiner points out, the image correction is the same as imaging the ratio of lactate to pyruvate or of lactate to alanine. Ans. 6–7.

We agree with the Examiner that "[g]iven that it was known that lactate builds up in tumors and its ratio to other metabolites such as lactate/pyruvate or lactate/alanine was . . . already used to identify tumors, it seems obvious that imaging this ratio would predictably yield good contrast for tumor tissues." *Id.* at 7.

With respect to Appellants' argument that there is not motivation to combine the references, again we are unpersuaded. One skilled in the art would have been motivated to combine the teachings of the references to improve and enhance the imaging techniques taught in Hara and Ardenkjaer-Larson. Non-Final Act. 6–7.

We conclude that a preponderance of the evidence supports the Examiner's conclusion that claim 1 would have been obvious over Hara combined with Ardenkjaer-Larson, Poptani, and Busch.

Turning to claims 2, 4–6, 10, and 11, while Appellants have discussed the rejection of these claims separately, the arguments mirror those discussed above. Appeal Br. 11. Thus, these claims fall with claim 1.

As to the rejections based on Hara, Ardenkjaer-Larson, Poptani, Busch and Gibson and Hara, Ardenkjaer-Larson, Poptani, Busch, Gibson and King, Appellants again rely on their arguments with respect to Hara, Ardenkjaer-Larson, Poptani, and Busch alone, arguing that the additional references do not correct the deficiencies of the primary references. *Id.* at 11–14. For the reasons stated above, we affirm these rejections.

Ke Combined with Minko and Ardenkjaer-Larson

Issue

The issue with respect to this rejection is whether a preponderance of the evidence supports the Examiner's conclusion that claims 1, 2, 6, 9–13, and 17–19 would have been obvious over Ke combined with Minko and Ardenkjaer-Larson.

The Examiner finds that Ke teaches measuring metabolites and obtaining the ratio of the two metabolites. Final Act. 24. The Examiner finds that Minko teaches the use of lactate/pyruvate ratios and lactate/alanine ratios to identify tumors. *Id.* The Examiner finds that Ardenkjaer-Larson teaches acquiring MR images using hyperpolarized ^{13}C contacting agents such as pyruvic acid. *Id.* at 25. The Examiner concludes that

> [i]t would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine of the method for imaging and processing metabolism data disclosed by Ke and Minko with the methods for imaging metabolites such as pyruvate using hyperpolarization of ^{13}C and subsequent MRI disclosed by Ardenkjaer-Lars[o]n et al. The skilled artisan would have made this combination in order to detect tumors using a more specific 13C labeled marker with greater signal rather than the proton based methods of Ke and Minko.

Id. at 25–26.

Appellants contend that the combination of references does not teach the claimed invention and that the references cannot be practically combined. Appeal Br. 16–17.

Analysis

Again, we adopt the Examiner's findings of fact, reasoning on scope and content of the prior art, and conclusions set out in the Final Action and

Answer regarding this rejection. We find the Examiner has established that claim 1 would have been obvious over Ke combined with Minko and Ardenkjaer-Larson. Appellants have not produced evidence showing, or persuasively argued, that the Examiner's determinations are incorrect. Only those arguments made by Appellants in the Briefs have been considered in this Decision. Arguments not presented in the Briefs are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015). We address Appellants' arguments below.

We are unpersuaded by Appellants' argument that the references do not teach the limitations of the claims. We agree with the Examiner that

> Ke and Minko teach detecting the presence of tumors by measuring metabolic ratios to patients via MRI. The art specifically indicates to measure the ratios of lactate to pyruvate (lactate/pyruvate) and lactate to alanine (lactate/alanine) in tissues to identify tissues with a high ratio indicating them to be tumors. Ardenkjaer-Lars[o]n teaches that that one can analyze the metabolism of compounds by using hyperpolarized 13C enriched compounds such as 13C pyruvate. The 13C-pyruvate is metabolized to lactate and alanine and the ratio of the pyruvate to these metabolites indicates the presence of tumorous tissues as taught by Minko. Monitoring the metabolism of hyperpolarized 13C pyruvate was already known in the art given the teachings of Ardenkjaer-Lars[o]n, and monitoring the metabolism of compounds and comparing the ratio of the substrate and metabolite, in specific pyruvate/lactate and pyruvate/alanine ratios was all well known in the art. Using the methods of Ardenkjaer-Lars[o]n is merely the use of an improved method of monitoring a compounds metabolism for a well-known assay used to detect tumor tissues.

Ans. 18–19.

We are not persuaded by Appellants' argument that the combination of the references would not be practical. Appeal Br. 17. Appellants have offered no evidence or arguments why such a combination would not be

practical and the Examiner provides reasons why the combination would have been obvious.

We conclude that a preponderance of the evidence supports the Examiner's conclusion that claim 1 would have been obvious over Ke combined with Minko and Ardenkjaer-Larson.

Turning to claims 2, 6, 9–13, and 17–19, while Appellants have discussed the rejection of these claims separately, the arguments mirror discussed above. Appeal Br. 17, 18. Thus, these claims fall with claim 1.

As to the rejections based on Ke, Minko, Ardenkjaer-Larson, and Hara, on Ke, Minko, Ardenkjaer-Larson, Hara, and Poptani; and on Ke, Minko, Ardenkjaer-Larson, Hara, Poptani, and Gibson, Appellants again rely on their arguments with respect to Ke, Minko, and Ardenkjaer-Larson alone, arguing that the additional references do not correct the deficiencies of the primary references. *Id.* at 18–20. For the reasons stated above, we affirm these rejections.

SUMMARY

We reverse the rejection under 35 U.S.C. § 101.

We affirm the rejections under 35 U.S.C. § 103(a).

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED